



1 22 May 2012
2 EMA/HMPC/312890/2012
3 Committee on Herbal Medicinal Products (HMPC)

4 **Concept paper on non-pharmacopoeial reference**
5 **standards for herbal substances, herbal preparations and**
6 **herbal medicinal products / traditional herbal medicinal**
7 **products**
8 **Draft**

Discussion by HMPC Drafting Group on Quality	February 2012 April 2012
Adoption by Committee on Herbal Medicinal Products (HMPC) for release for consultation	22 May 2012
Start of public consultation	27 June 2012
End of consultation (deadline for comments)	15 October 2012

Comments should be provided using this [template](#) to hmpc.secretariat@ema.europa.eu

Keywords	HMPC; herbal medicinal products; traditional herbal medicinal products; herbal substances; herbal preparations; reference standards; primary standards; secondary standards; constituents with known therapeutic activity; active markers; analytical markers; non-pharmacopoeial reference standards
----------	---

9



10 **1. Introduction (background)**

11 This concept paper applies to non-pharmacopoeial reference standards for herbal substances, herbal
12 preparations and herbal medicinal products (HMPs) / traditional herbal medicinal products (THMPs).

13 The quality of herbal medicinal products should be guaranteed and demonstrated in accordance with
14 the existing requirements as set out in Annex I of Directive 2001/83/EC, as amended, with specific
15 herbal quality guidelines such as 'Guideline on quality of HMPs/THMPs' (EMA/CPMP/QWP/2819/00 Rev.
16 2) (EMA/CVMP/814/00 Rev. 2), 'Guideline on specifications: test procedures and acceptance criteria for
17 herbal substances, herbal preparations and HMPs/THMPs' (EMA/CPMP/QWP/2820/00 Rev. 2)
18 (EMA/CVMP/815/00 Rev. 2), 'Guideline on quality of combination HMPs/THMPs'
19 (EMA/HMPC/CHMP/CVMP/214869/2006) and, in addition, with current EU/ICH general quality
20 guidelines for medicinal products that are applicable to HMPs/THMPs.

21 Reference standards play an essential role when ensuring and demonstrating adequate and consistent
22 quality of herbal substances, herbal preparations and HMPs/THMPs. These reference standards may be
23 a botanical sample of the herbal substance, a sample of the herbal preparation (e.g. extract or
24 tincture) or a chemically defined substance e.g. a constituent with known therapeutic activity, an
25 active marker or an analytical marker etc.

26 In the European Pharmacopoeia (Ph. Eur.) monographs on herbal substances and herbal preparations,
27 pharmacopoeial reference standards are described for a specific purpose and they are only
28 demonstrated to be suitable for the use indicated. Where pharmacopoeial reference standards are
29 available they should be used as primary standards.

30 In cases, where pharmacopoeial reference standards are not available, non-pharmacopoeial reference
31 standards should be established.

32 The purpose of the proposed guideline is to identify the criteria to be taken into account when using
33 non-pharmacopoeial reference standards and to provide guidance on the documentation needed to
34 demonstrate that they are adequately characterised and suitable for their intended purpose.

35 **2. Scope**

36 The concepts described in the proposed guideline will be applicable to registration applications for
37 THMPs for human use and will also be applicable to marketing authorisation applications for HMPs for
38 human and veterinary use.

39 **3. Problem statement**

40 Active substances (herbal substance(s) and/or herbal preparation(s)) in HMPs consist of complex
41 mixtures of phytochemical constituents. To ensure adequate quality control, reference standards are
42 necessary for their identification, purity testing and assay.

43 Existing guidelines provide only limited guidance on non-pharmacopoeial reference standards (e.g. on
44 'Specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and
45 HMPs/THMPs'). As a result, the choice of these non-pharmacopoeial reference standards, their
46 production and the quality documentation provided vary between applicants/manufacturers, even for
47 similar products.

48 **4. Discussion (on the problem statement)**

49 A non-pharmacopoeial reference standard may be a botanical sample of the herbal substance, a
50 sample of the herbal preparation (e.g. extract or tincture) or a chemically defined substance e.g. a
51 constituent with known therapeutic activity, an active marker or an analytical marker etc.

52 Chemically defined substances are either commercially available or they have to be isolated and
53 purified. However, in every case, as described in Ph. Eur. Chapter 5.12., detailed documentation on the
54 structural elucidation and the purity should be provided, especially if the reference standard is intended
55 for an assay. These substances can be used as primary or secondary standards.

56 A guideline on non-pharmacopoeial reference standards should describe in detail the documentation
57 that the applicant should provide in order to demonstrate that the reference standard is adequately
58 characterised and meets quality standards appropriate for its intended use.

59 **5. Recommendation**

60 As there is very little information on reference standards in the existing guidelines, the HMPC
61 recommends the development of a respective guideline.

62 A guideline on non-pharmacopoeial reference standards for herbal substances, herbal preparations and
63 HMP/THMPs should describe the information to be provided in Module 3 sections 3.2.S.5. and 3.2.P.6.
64 'Reference standards or materials'.

65 This guideline shall apply to THMPs for human use and to HMPs both for human and veterinary use.

66 **6. Timetable**

67 It is anticipated that a draft guideline could be available one year after publication of the concept
68 paper. The draft guideline will be released for external consultation for six months. The guideline could
69 be finalised within six months after external consultation.

70 **7. Resource requirements for preparation**

71 The Rapporteur and Co-Rapporteur should prepare a draft guideline. Members States are invited to
72 provide comments via their Committee and/or Working Party Members.

73 **8. Impact assessment (anticipated)**

74 The development of this guideline on non-pharmacopoeial reference standards is expected to benefit
75 industry. When non-pharmacopoeial reference standards need to be used, this guideline will clarify the
76 information to be submitted in Module 3 (sections 3.2.S.5. and 3.2.P.6. 'Reference standards or
77 materials'), taking account of the nature of the non-pharmacopoeial reference standard, its intended
78 use, production, labelling and storage. This will therefore provide benefits to applicants in the
79 preparation of their applications.

80 The guideline is also expected to help competent authorities when assessing applications by
81 harmonising requirements and thus enabling a more consistent approach to assessment of the
82 documentation.

83 9. Interested parties

84 During the consultation period on the draft guideline, comments from parties concerned with the use of
85 THMPs and HMPs will be welcome.

86 10. Definitions

87 **Characteristic constituents** are chemically defined substances or groups of substances that are
88 specific for a medicinal plant and can be used for identification purposes.

89 **Constituents with known therapeutic activity:** are chemically defined substances or groups of
90 substances, which are generally accepted to contribute substantially to the therapeutic activity of a
91 herbal substance, a herbal preparation or a herbal medicinal product.

92 **Herbal medicinal products:** any medicinal product, exclusively containing as active substances one
93 or more herbal substances or one or more herbal preparations, or one or more such herbal substances
94 in combination with one or more such herbal preparations.

95 **Herbal preparations:** are obtained by subjecting herbal substances to treatments such as extraction,
96 distillation, expression, fractionation, purification, concentration or fermentation. These include
97 comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and
98 processed exudates.

99 **Herbal substances:** all mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an
100 unprocessed, usually dried form but sometimes fresh. Certain exudates that have not been subjected
101 to a specific treatment are also considered to be herbal substances. Herbal substances are precisely
102 defined by the plant part used and the botanical name according to the binomial system (genus,
103 species, variety and author).

104 **Impurity:**

105 (1) Any component of the herbal substance, which is not the entity defined as the herbal substance.

106 (2) Any component of the herbal preparation/herbal medicinal product that is not the entity defined as
107 the herbal substance/ preparation or an excipient in the herbal preparation/herbal medicinal product.

108 **Markers:** are chemically defined constituents or groups of constituents of a herbal substance, a herbal
109 preparation or a herbal medicinal product which are of interest for control purposes independent of
110 whether they have any therapeutic activity. Markers serve to calculate the quantity of herbal
111 substance(s) or herbal preparation(s) in the herbal medicinal product if the marker has been
112 quantitatively determined in the herbal substance or herbal preparation.

113 There are two categories of markers:

114 *Analytical markers* are constituents or groups of constituents that serve solely for analytical purposes.

115 *Active markers* are constituents or groups of constituents, which are generally accepted to contribute
116 to the therapeutic activity.

117 **Reference standard:** is a general term covering reference substances, reference preparations and
118 reference spectra, used as a standard in an assay, an identification or a purity test.

119 **Primary standard:** A standard shown to have suitable properties for the intended use, the
120 demonstration of suitability being made without comparison to an existing standard.

121 **Secondary standard:** A standard established by comparison with a primary standard.

122 **Specification:** A list of tests, references to analytical procedures, and appropriate acceptance criteria,
123 which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of
124 criteria to which a herbal substance/preparation or herbal medicinal product should conform to be
125 considered acceptable for its intended use. "Conformance to specifications" means that the herbal
126 substance/preparation and/or herbal medicinal product, when tested according to the listed analytical
127 procedures, will meet the listed acceptance criteria. Specifications are binding quality standards that
128 are agreed to between competent regulatory authorities and applicants.

129 **Traditional herbal medicinal products:** are medicinal products for human use that fulfil the
130 conditions laid down in article 16a (1) of Directive 2001/83/EC, as amended.

131 **Unidentified impurity:** an impurity which is defined solely by qualitative analytical properties, (e.g.,
132 chromatographic retention time).

133 **11. References**

134 - 'Guideline on quality of herbal medicinal products/traditional herbal medicinal products'.

135 (EMA/CPMP/QWP/2819/00 Rev. 2), (EMA/CVMP/814/00 Rev. 2).

136 - 'Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal
137 preparations and herbal medicinal products/traditional herbal medicinal products'.

138 (EMA/CPMP/QWP/2820/00 Rev. 2), (EMA/CVMP/815/00 Rev. 2).

139 - 'Guideline on quality of combination herbal medicinal products / traditional herbal medicinal
140 products'. (EMA/HMPC/CHMP/CVMP/214869/2006).

141 - 'Reflection paper on markers used for quantitative and qualitative analysis of herbal medicinal
142 products and traditional herbal medicinal products'.

143 (EMA/HMPC/253629/2007).

144 - European Pharmacopoeia Chapter 5.12. 'Reference standards'.